REMARKS

This paper responds to an Office Action mailed June 5, 2003. Further to the Restriction Requirement, Applicants are withdrawing claims 2, 3, 8, 11, 12, 17 and 18, from consideration without prejudice to, or disclaimer of, any subject matter therein. In particular, Applicants retain the right to file divisional and/or continuation applications directed to any withdrawn subject matter. Claims 1, 4-7, 9, 10, 13-16 and 19-21 are currently pending.

Claims 1, 4-6, 9, 10, 13-16 and 19- 21 have been amended in part to remove reference to withdrawn claims. These claims do not include any amendments made for a purpose of narrowing scope or limiting the inventive subject matter other than amendments based on Applicants' election of certain embodiments and withdrawal of others from consideration. Other amendments are intended to clarify certain aspects of the invention already set forth in the claims.

It is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. Applicants respectfully submit that their application is now in condition for allowance.

I. OBJECTIONS AS TO FORM

The Office has objected to use of abbreviations in the claims. Applicants disagree with this position, since abbreviations are perfectly acceptable if it is clear what they mean. In any case, Applicants have removed "MAPK as part of their amendments. However, they have inserted in its place the term "MEK enzyme." With the first use of "MEK" in claim 1, Applicants have provided a fuller name for this enzyme, (MAPK/ERK kinase), which, granted, is also abbreviated. These abbreviations are all set forth in the specification and have been used routinely in the art for over 20 years. It is believed that the claims are in proper form with respect to their use of abbreviations and that this objection should be withdrawn.

The Examiner objected to claim 9 because the term "sum of the products" is allegedly confusing (but did not invoke a §112, second paragraph rejection). Applicants fear that the Examiner has been confused by the term "products," believing this to refer to some sort of biological or chemical product. Rather, the term "product" here is used in its mathematical sense, as the number obtained when multiplying two other numbers (the multiplicand and the multiplier). In measuring tumor size, it is common to measure two perpendicular diameters of each lesion, multiply them to obtain a "product" and then to add these products for each individual lesion, so

that the sum of these "products" is a measure of total body tumor size or mass. This is how the term is used in claim 9, which, incidentally, has been amended for greater clarity by reciting "50% decrease in tumor size measured as..." It would thus be proper to withdraw this objection.

The Office has objected to the term " "characterized by" in claim 9. While Applicants believe that this is a perfectly acceptable and definite term as it was used, they have amended claim 9 more extensively and, with that amendment, have removed "characterized" and used the term "comprises" suggested by the Examiner when referring to the criteria for the claimed antitumor response.

Claims 6, 15 and 21 have been amended to depend only from elected claims, so any improper dependencies have been removed.

II. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH: WRITTEN DESCRIPTION

The Office rejected all pending claims under 35 U.S.C. § 112, first paragraph, as lacking adequate written description.

A. The Standard

The standard for a rejection based on inadequate written description was set out by the Federal Circuit in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) (quoting *In re Smith*, 178 USPQ 620, 623-624 (CCPA 1973)):

> In order to determine whether a prior application meets the "written description" requirement with respect to later-filed claims, the prior application need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the earlier date the applicant had invented what is now claimed.

See, also, *In re Wertheim*, 191 USPQ 90, 98 (CCPA 1976) ("Lack of literal support . . . is not enough . . . to support a rejection under §112."). The *Wertheim* court further pointed out, *supra* at 96, that

> The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material. (*In re Smith*, 178 USPQ 620)... It is not necessary that the application describe the claim limitations exactly, *In re Lukach,* 169 USPQ 795 (1971), but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations. *In re Smythe...* 178 USPQ 279,284 (CCPA 1973).

B. The Rejection

Applicants are somewhat confused by the formulation of the Office's grounds for rejection, and the conflation of issues that concern enablement and scope with those of written description. Specifically, it has been alleged that the claims are directed to embodiments (in the form of anti-melanoma agents) that are completely unrelated structurally to one another so that the disclosure of the various types of MEK inhibitors ("inhibitors of the MAPK pathway") does not adequately describe "the scope of the claimed genus," which, in the Office's view " encompasses a **substantial variety** of subgenera of pathway inhibitors or small organic molecules. According to the Office, the specification "fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of inhibitors." Because the disclosure allegedly fails to describe the "common attributes or characteristics" that identify members of the genus, which are allegedly "highly variant," then, according to the Office, the specification is "insufficient to describe the genus inhibitors that induce apoptosis or are cytotoxic to melanoma cells." The Office contends that one of skill in the art would reasonably conclude that the disclosure fails to provide a "representative number of species" to describe and enable (here the Office appears to be confusing or conflating the independent requirements under §112, first paragraph) the genus as broadly claimed (again, conflating "scope" with "written description")

C. Applicants' Response

Applicants believe that the Office has not met its burden, as noted above, for a *prima facie* case of lack of adequate written description. Moreover, Applicants believe that the Office's reliance on the *Regents of the University of California v. Lilly* case and the use of analogies to DNA sequences are not particularly applicable to the present case. Part of the difficulty appears to lie in the fact that the instant specification described two broad classes of agents that act against melanoma and induce similar effects: (a) proteins and (b) small organic molecules. These two classes of molecules were separated by the Office's restriction. In view of Applicants' election of claims based on the use of small organic molecules, and the amendments made herein as a result of the election, the Office's perspective may be assisted by the following discussion. A second factor affecting the Office's understanding of the invention appears to result from the fact that the organic small molecule inhibitors of MEK do not fall into any neat "structural package" that the Office seeks to identify in order to feel comfortable with the genus or subgenus that the Applicants seek to claim (*e.g.*, amended claims 1 and 4).

Restatement of the Key Elements of the Invention

Applicants wish to emphasize at the outset that these anti-melanoma agents, both the proteins and the small organic molecules, do have something very important in common. They are all inhibitors (or "inactivators" of the MEK enzyme). By inhibiting MEK action, they cause inhibition of the MAPK pathway which has an unexpected outcome in melanoma cells. Applicants have discovered for the first time that different types of molecules that inhibit the action of MEK cause melanoma cells, particularly human melanoma cells, to undergo apoptosis and die. This is very unusual because these types of molecules, that inhibit the same enzyme and pathway in other types of tumor cells, have been found to be only cytostatic towards those cells, but not **cytotoxic.** (See specification, at page 1, line 26 to page 2, line 2.) This distinction cannot be emphasized enough, because it makes the difference between (a) a true kill-off of tumor cells, vs. (b) the mere slowing of their proliferation, leaving the tumor cells alive and able to begin to proliferating again later (something a dead tumor cell cannot do, even in its wildest dreams).

An additional feature that is common to the small molecule inhibitors of the present invention is that they are all ***noncompetitive*** inhibitors of MEK. In other words, they do not inhibit the binding of the enzyme to one of its substrates, adenosine triphosphate (ATP), which is the source of the phosphate group that is transferred to the other MEK substrate, the MAPK/ERK protein. Moreover, some of these MEK inhibitors have been shown to share a common (or overlapping) binding site in MEK (*e.g.*,, PD098059 and U0126 as described in, Favata, M.F. *et al.*, "Identification of a novel inhibitor of mitogen-activated protein kinase kinase," *J Biol Chem.* 1998, 273:18623-32 ("Favata"), see, *e.g.*, page 18623, Abstract, lines 7-9 and 13-22; page 18628, column 1, second full paragraph; page 18629, column 1, last paragraph; and page 186320, first partial paragraph). **A copy of this reference is attached hereto as it was not yet made of record.**

This **noncompetitive** mode of inhibition of all the small molecule inhibitors described and claimed here (a fact well-known in the art, though not explicitly stated in the specification) is a common feature that sets them apart as a genus or subgenus from *nearly all other kinase inhibitors* which are ATP-competitive. See, *e.g.,* Cohen, P., *Curr Opin Chem Biol.* 1999, *3*:459-465 (of record in this case) at page 463, column 1, last paragraph. Thus, the compounds PD184352, PD98059 and U0126, are a rather unusual subgenus of kinase inhibitors in that they are direct, but noncompetitive, inhibitors of MEK. See, Favata, *supra*, and Sebolt-Leopold, J.S. *et al.*, "Blockade of the MAP kinase pathway suppresses growth of colon tumors *in vivo*," *Nature Medicine*, 1999,

5:810-816 ("Sebolt-Leopold"), also of record in this case (at page 810, column 1, last paragraph-column 2, first partial paragraph).

Finally, it is worth noting, that the proteins that prevent MEK activity (claims to which have been withdrawn), such as anthrax lethal factor ("LF" or "LeF"), also lead to inhibition of the MEK enzyme in a direct and noncompetitive manner because these inhibitors are proteases which specifically cleave MEK. Although not considered classically to be "enzyme inhibition" in the kinetic sense, the result is the same – loss of MEK activity and, as a consequence, downregulation of the MAPK pathway. In view of these points, it should now be evident why these structurally diverse molecules have the same net result that appears to be rather selective towards melanoma cells (and tumors) – induction of apoptosis and cytotoxicity (vs. cytostasis). This is at the center of the present invention.

Further Remarks and Conclusion

When the invention is viewed in this light, considering what is known in the art about MEK and its inhibitors, it is evident that the Office's reading of the specification requires some modification, and its view of the adequacy of the written description for the claims as amended, should be altered significantly.

Specifically, amended independent claims 1, 9 and 16 are directed, respectively to methods of killing melanoma cells (claim 1) , inducing an antitumor response in a mammal having melanoma (claim 9) or inhibiting growth or recurrent growth of melanoma tumors (claim 16) , comprising administering an effective amount of an organic small molecule MEK inhibitor, which evokes a selective cytotoxic response by inducing apoptosis in the melanoma cells. Moreover, three different MEK inhibitors, PD184352, PD 98059 and U0126 have been tested by Applicants or by others either *in vitro*, *in vivo*, or both, in such a way that the present disclosure viewed in the context of what is known in the art certainly complies with the written description requirement of §112, first paragraph.

Again, Applicants reiterate that, in general, inhibitors of signal transduction pathways, including the MAPK pathway, are cytostatic in nature, merely arresting the growth of tumor cells but not killing them (*e.g.*, specification, page 1, line 26-page 2, line 2). However, the present inventors have discovered that a group of molecules that inactivate or inhibit MEK directly and noncompetitively, including MEK- directed proteases, such as *Bacillus anthracis* LF, and certain small molecule pharmacological MEK inhibitors, such as PD184352, PD98059 and U0126, display

particularly potent and selective action on human melanoma cells. Indeed, a large number of melanoma lines have been tested as supported by results in the NCI-ADS database and the Applicants' own research. See specification at page 2, lines 3-12.

When testing each of the three compounds recited in claims 4. 13 and 19, as detailed below, the inventors found that the inhibition of MAPK signaling through MEK selectively inhibited the growth of human melanoma cells on the one hand (page 2, lines 14-15) which is not unique to melanoma, and triggered an apoptotic and cytotoxic response in these cells which is unique and selective. Thus, there was no such apoptotic response in normal melanocytes or in other tumor cell types (page 2, lines 23-25).

Thus, it is fair to conclude that the present disclosure provides adequate written description to support the more generic claims presently pending which have been amended from their original form. Therefore it would be proper to withdraw this rejection under 35 U.S.C. § 112, first paragraph.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH: LACK OF ENABLEMENT

The Office rejected all pending claims under 35 U.S.C. § 112, first paragraph, as lacking in enablement for the scope claimed.

It respectfully is submitted that when the proper test for enablement is applied to the pending claims, considered in light of the respective burdens upon an applicant for patent and the Patent Office in establishing and responding to a *prima facie* case of nonenablement, the claims should be found to be enabled and allowable.

A. Legal Test for Enablement:

The enablement requirement of § 112 ensures that one skilled in the art will be able to make and use a claimed invention. *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 599 (Fed. Cir. 1983). That some experimentation may be required does not preclude a finding of enablement so long as the amount of experimentation is not unduly extensive. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 316 (Fed. Cir. 1983). Furthermore, there is "no magical relation between the number of representative examples and the breath of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'"

In re Borkowski, 164 USPQ 642, 646 (CCPA 1970). A specification, in fact, need not contain a single working example. Id. 164 USPQ at 645.

The Office has the burden of establishing a lack of enablement. *In re Hogan*, 194 USPQ 527, 539 (CCPA 1977). Factors to be considered in determining whether pending claims would require undue experimentation have been articulated by the Court of Appeals for the Federal Circuit in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). They include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In this case, the Office Action has not set forth adequate evidence through clear, factor-by-factor, Wands analysis to demonstrate that one skilled in the art would find the specification nonenabling in light of its discussion and exemplification. Applicants fail to find an adequate Wands analysis lurking among the wide-ranging set of remarks offered by the Office, as they will detail below. Hence, the Office Action has not provided the Applicants with an assessment of enablement under the "standard of reasonableness" to which they are entitled, given the nature of the invention and the state of the art.

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. [citations omitted] The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed... .

In re Jackson, 217 USPQ 804, 807 (Bd. App. 1982, cited with approval in *Wands*, 8 USPQ2d at 1404).

Even when "unpredictability" in a field such as chemistry may create reasonable doubt as to the accuracy of a broad statement supporting enablement, and even when the statement is, on its face, contrary to generally accepted scientific principles, the Court of Customs and Patent Appeals (predecessor to the U.S. Court of Appeals for the Federal Circuit), clearly articulated that

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with a contested statement.

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1967).

B. Specific Grounds of Rejection:

The Office's analysis concluded with the following statements about enablement that indicates a failure to appreciate the "nature of the invention" (one of the Wands factors) and the state of the prior art with respect to the compounds disclosed and claimed (another Wands factor).

> [I]t is unpredictable that PD184352 could induce apoptosis of melanoma cells, or killing melanoma cells or induce antitumor response in a patient. In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Applicants contend that the specification does provide sufficient support for the claimed invention, as defined by the amended claims. The following discussion of the record in this case follows the illustrative approach to assessing enablement from the *Wands* opinion.

(1) ***the quantity of experimentation necessary***

The Office Action did not quantify the amount of experimentation necessary, but rather merely stated that PD184352 was not tested *in vivo* and then proceeded to an "unpredictability" analysis. As discussed in more detail below and applying the standard of reasonableness developed by the PTO Board in *Jackson* (as adopted in *Wands*), the specification does provide enabling experimentation and description to enable one skilled in the art to make and use the invention as set forth in the presently amended claims.

There is no evidence or compelling rationale of record in this case that the nature of the invention and the state that inherently require an unreasonably excessive amount of experimentation, or that additional or alternative test protocols are necessary to practice Applicants' invention, or that one skilled in the art could not readily implement the methods described in the specification.

(2) ***the amount of direction or guidance presented***

There is nothing in the record to evidence or explain in a compelling way why sufficient direction or guidance is not presented. The Office Action did not provide any basis to fault specifically the amount of direction or guidance presented in the specification.

As discussed below, there is ample direction and guidance to enable one skilled in the art to practice the invention

(3) ***the presence or absence of working examples***

Contrary to the Office's contentions, several working examples are present. The Office alleges that Example X on pages 56-57 is unclear as to whether the example relates to use of a MEK protease such as LF, a small molecule MEK inhibitors, or both at the same time. Further, the Office contends that the specification lacks disclosure of which small molecule inhibitor is used for the treatment, nor is there any actual treatment data using PD184352 alone. The Office Action further states that although the specification discloses the dosage of the lethal factor (LF) protein for *in vivo* killing melanoma cells (p. 56), no disclosure is found for the dosage of the organic small molecule PD184352 necessary for the treatment. Finally, the Office asserts that the specification lacks guidance on the dosage necessary for the treatment, and schedules of treatment, using the small organic molecule PD184352.

As discussed below, there are several working examples as well as prophetic examples that enable one skilled in the art to make and use the invention.

(4) ***the nature of the invention***

The Office Action never specifically discussed the "nature of the invention" as a whole. Rather it reiterated claim language multiple times to the point of being confusing to Applicants, while presenting only broad statements that the field of the invention is complex and unpredictable. However, there is no evidence or compelling argument to support a finding that the invention is so technically complex that one skilled in the art could not practice the invention as it is disclosed and exemplified in the specification.

In addition, as discussed in more detail below, the Office appears to have misunderstood the purpose and results of Example IV (page 48, lines 17-18, Figs. 5A, 5B, 6 and 8) leading to an incorrect conclusion that only a certain specific level of reduction of the ERK1/2 enzymes of the MAPK pathway, **but not any level of reduction ,** correlated with apoptosis. This led to a conclusion that Applicants do not understand: that "due to possible homeostasis regulation, one cannot predict that PD184352 would reduce ERK1/2 enzymes to a specific level in melanoma cells *in vivo* that is effective for inducing apoptosis.

(5) ***the state of the prior art***

The Action does not provide evidence or compelling rationale why the art of cancer therapy is so inherently complex that it does not permit application of information gathered from accepted *in vitro* and animals studies to support claims to killing of cancer cells or therapeutic effects on tumors. The areas of cancer therapy and signal transduction are well studied, and the state of the art is advanced on many fronts.

Rather, the Office Action recites a number of "off-the-shelf" arguments based on an incomplete view of the application as a whole, an undervaluation of the amount of knowledge that exists about the specific compounds (and classes of compounds) the use of which are claimed, and fails to give adequate credit to the utility and acceptability (both in the scientific community and in the patent law) of *in vitro* models and animals models that are supportive of claims directed to killing of cancer cells or treating tumors. For example, the Office Action states characteristics and responses of cells in culture to drugs are different from characteristics and responses of cells to drugs in primary cancer tissues, due to a variety of effects which are absent in *in vitro* conditions. It is contended that the cited references – most of which are 20-30 years old - show evidence of the contradictions between "life on the bottom of a lab dish" and in the body. The Office Action concludes that it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and that cultures cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

However, the Applicants believe that some credit is due to advances in the field of cancer therapy, including immunotherapy, over the last 20 -30 years. Moreover, as discussed below, consideration of the invention in view of the application as a whole including the working examples as well as an understanding of small organic MEK inhibitor compounds would reasonably lead a skilled person to conclude that the invention is enabled.

(6) ***the relative skill of those in the art***

The Action does not provide any analysis of the ordinarily skilled artisan, which Applicants assert is that of a Ph.D. or M.D. scientist with several years of postdoctoral research experience. In much of the analysis and citation of references, the Office relies on publication that are 20-30 years old.

(7) ***the predictability or unpredictability of the art***

According to the Office Action, one cannot extrapolate the teachings of the specification to the claims because it is allegedly well known that the art of anticancer drug discovery is highly unpredictable, since "many thousands of drugs" have shown activity in either cell or animal models but very few have actually been shown to be useful for chemotherapy. The Office further contends that tumors resist penetration by drugs and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors.

The Office Action concludes that it is clear, based on the state of the art, in the absence of experimental evidence, that no one skilled in the art would accept the assertion that the method comprising the administration of PD184352 would function as claimed.

Applicants contend to the contrary that there is adequate support in the form of experimental evidence in the specification and the art of record (*e.g.*, the Sebolt-Leopold reference) that establishes a basis for the skilled artisan to accept the enablement of the present claims.

(8) **the breadth of the claims**

The Office Action does not adequately address in the breadth of the claims, but rather merely reiterates the fact that claims 1, 4-7, 9-10, 13-16, 19-21 are drawn to a method for killing melanoma cells, or inducing an antitumor response in a mammal having melanoma, or inhibiting growth or recurrent growth of a melanoma tumor in a mammal having melanoma, comprising administering an inhibitor of the MAPK pathway, which is the organic small molecule PD184352 and that PD184352 was not tested *in vivo*.

There is no evidence or compelling rationale in the record of this case to support a finding that the breadth of the claims as amended, exceeds the enablement provided by the specification in view of the state of the art.

C. **Specific Response to the Enablement Rejection:**

It is respectfully submitted that the Office Action has not set forth a *prima facie* case of nonenablement and that based on the "partial" Wands analysis as discussed above, the Office rejected all pending claims for lack of enablement of the scope claimed. This was predicated in

large part on the Office's contention, *inter alia*, that the specification lacks examples of the use of PD184352 in treating melanoma in humans and what appears to be an incomplete understanding of the invention. Based on the foregoing analysis and assessed in light of the "standard of reasonableness" to which the claims are legally entitled, given the nature of the invention and relative state of the art of signaling pathways and their disruption for cancer therapy, it would be appropriate to reverse the § 112 rejection.

As noted above, the amended claims are directed to administering a member of a family of MEK inhibitors, with emphasis on PD184352 (in particular), PD98059 and U0126, to kill melanoma cells *in vitro* or *in vivo*. Each of these compounds and its properties is described in the specification and the prior art. The inventors found that sustained inhibition of MAPK signaling in human melanoma cells produced by inhibiting MEK enzymatic activity, resulted in a melanoma-selective apoptotic and cytotoxic response. This provides an adequate basis for claims having the present scope. It is worth noting again that the Sebolt-Leopold reference (of record) discloses that PD184352, by inhibiting MEK and thereby the MAP kinase pathway, resulted in a number of cellular and therapeutic outcomes. Among them was the impairment in the growth *in vivo* of mouse and human colon tumors. More than that, this agent affected cell scattering, a correlate of invasiveness and metastatic potential. All this occurred in cells to which PD184352 is merely cytostatic, not cytotoxic. Therefore, a person skilled in the art would expect this compound to do as much, if not more, to a tumor the cells of which it could kill. This reference states at page 814, column two, beginning of the first full paragraph: "The full scope of tumor types that rely most heavily on MAPK activation for their proliferative and invasive properties remains to be explored." What the Applicants have done is to identify a different tumor type, melanoma, which not only is more reliant on MAPK activation for the properties noted above but actually **depends on MAPK activation for its very survival**. This leaves little room for doubt as to the effectiveness and selectivity that one of skill in the art would expect of PD184352 and the other disclosed MEK inhibitors in (a) killing melanoma cells, (b) mediating an antitumor response in a mammal, particularly a human, having melanoma, and (c) inhibiting growth, including recurrent growth, of melanoma tumor cells in a mammal. These effects would be expected to be selective for melanoma and sparing of normal melanocytes because, as shown by the inventors, MEK inhibition does not have cytotoxic consequences on normal human melanocytes, even though it completely blocks the

activation of MAPK in these cells, arresting them in G1. However, no apoptosis was ever detected even after prolonged inhibition (specification at page 4, lines 26-29).

One of the Applicants' observations was that MEK inhibition stimulated melanin production (a normal melanocyte function) in melanoma cells thus mimicking a phenotype associated with differentiated melanocytes. cAMP-elevating agents (including both the anthrax bacillus product, "edema factor" (EF), a protein complex, and the small molecule isobutylmethylxanthine (IBMX)) are known to induce differentiation accompanied by melanin production in melanoma cells. It is important to note, however, that even though EF and IBMX synergize with MEK inhibitors in their stimulation of melanin production, both these cAMP-elevating agent dominantly antagonize the apoptosis induced by MEK inhibitors (page 4, lines 20-25; see also, Example IV). This should put to rest the concern and confusion expressed in the Office Action with regard to the existence of a correlation between "specific levels of reduction of ERK1/2 enzymes ...but not any level of reduction" and apoptosis (*in vitro*). There is no such thing here: MEK inhibition kills melanoma cells, and concomitant elevation of cAMP in these cells antagonizes this effect. The specification showed clearly that apoptosis in melanoma cells was not a mere "byproduct" of the differentiation induced by inhibiting MAPK signaling (*e.g.*, page 48, lines 25-28; Figs. 5A, 5B, 6 and 8; Example IV, page 48, lines 17-18).

To reiterate some of the observations disclosed in the specification (or reported in the literature) using direct, noncompetitive small molecule MEK inhibitors:

(1) **PD98059** induced apoptosis by inhibiting the MAPK pathway in human melanoma cells (*e.g.*., Figs. 2 and 3E-3G; Example II, page 46, lines 20-21; Example III, page 47, lines 11-13; Table 4; Table 5).

(2) **PD98059** inhibited ERK 1 and 2 (Fig. 4, Example III, page 47, lines 15-16) and blocked cell cycle progression in G1 (Figs. 3B and 3E; Example III, lines 10-11).

(3) MEK inhibitor **PD184352** induced apoptosis in melanoma cells but not in normal melanocytes (Table 5). The selective cytotoxicity of PD184352 to human melanoma cells in comparison to normal human melanocytes is due to dose-dependent apoptosis, with activity possibly several fold higher than PD98059 (page 50, lines 1-4). Western blot analysis with a phospho-specific anti-ERK antibody confirmed that activation of MAPK (ERK1/2) was completely blocked by PD184352 in M14-MEL melanoma cells (page 50, lines 5-6).

(4) **U0126** induced apoptosis in human melanoma cells (Fig. 15, Example II, page 46, lines 24-25; Table 4).

(5) Similar to the above results, MEK-directed protease **LF** was also shown to induce apoptosis by inhibition of the MAPK pathway in human melanoma cells (e.g., Figs. 1 and 3C-3F; Example II, page 46, lines 20-21; Example III, page 47, lines 11-13; Table 4). LF inhibited ERK 1 and 2 (Fig. 4, Example III, page 47, lines 15-16) and blocked cell cycle progression in G1 (Figs. 3B and 3E; Example III, lines 10-11). **LF** was shown to inhibit the MAPK pathway in normal human primary melanocytes, but not to induce apoptosis (Figs. 10, 11A-11D; Example V, page 50, lines 10-12). LF completely inhibited ERK activation but did not cause apoptosis (Fig. 9; Example V, page 50, lines 13-14) as compared to LF triggering apoptosis in melanoma cell lines (Fig. 11D; Example V, lines 14-15).

(6) Both **PD98059** (Figs. 12A-12D and 13; Table 5, Example V, page 50, lines 10-12) and **U0126** (page 8, lines 9-10) had similar effects as described in (5), and PD98059 inhibited ERK activation without causing apoptosis in normal melanocytes (Fig. 9; Example V, page 50, lines 13-14).

(7) The *in vivo* effects of stopping MEK activity, demonstrated using LF (as a MEK protease), reduced the size of melanoma tumors, and significantly attenuated the growth of tumors even when it was given systemically (Examples VII-IX, pages 52-55; Figs. 14, 16-21).

(8) Prophetic Example X, pages 55-57 was based on predicted results calculated from the "working" *in vitro* Examples II-VI and "working" *in vivo* Examples VII-IX. [See: MPEP 2164.03] Example X is directed to the use of anti-melanoma agents in humans *in vivo*: the agents contemplated included all members of the two general classes of therapeutic compositions including each of the small molecule MEK inhibitors.

A fair reading of the application as a whole including the prior nine Examples would clarify to one skilled in the art that, in Example X, Applicants envisioned the outcome of treating a subject independently with PD98059, U0126 or PD184352. Moreover, the specification does set forth a schedule of dosages for small molecule MEK inhibitors which clearly includes PD184352, see page 56, lines 9-13, which reads as follows:

> (2) Small Molecule MEK inhibitors
>
> A treatment consists of injecting the patient with 1, 100 or 1000 μg of protein or polypeptide intravenously in 200 ml of normal saline over a one-hour period. Treatments are given 3x/week for a total of 12 treatments. Patients with stable or regressing disease are treated beyond the 12th treatment. Treatment is given on either an outpatient or inpatient basis as needed.

Applicants remind the Office that according to MPEP 2164.02, an example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved. The experiments and administration of the compounds set forth in application are fully and adequately disclosed in such manner that one skilled in the art will be able to practice the invention to the full extent of the claim scope without requiring undue experimentation. Applicants need not describe every embodiment in order for the disclosure to be enabling.

When considering the factors relating to a determination of enablement, if all the other factors point toward enablement, then the absence of a working Example will not by itself render the claims non-enabled.

The patent law recognizes the importance of a correlation between *in vitro* results and predicted *in vivo* action of a biological or chemical agent, and this is related to the issue of the presence or absence of working examples. An *in vitro* or *in vivo* animal model exemplified in the specification constitutes a "working example" if that example "correlates" with a disclosed or claimed method. Obviously, the impact of such "correlation" also depends on the state of the prior art. If a particular *in vitro* or animal model is recognized as being correlated to a specific condition, as in the case of melanoma cell lines *in vitro* or growing a tumor xenografts in mice, then it should be accepted as correlating unless the Examiner can come forth with evidence for a lack of correlation. Even with such evidence, the Office must weigh the evidence for and against a correlation and set forth whether one skilled in the art would accept the model as reasonably correlated to the condition. See: *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). In view of the initial burden on the Office to give reasons for the lack of enablement, an Examiner must also give the Applicant the reasons for concluding that an *in vitro* or *in vivo* animal model example lacks the requisite correlation. There is no hard and fast rule as to how invariable or exact the correlation must be (*Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Based upon the relevant evidence as a whole, a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity will be found even absent rigorous correlation where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

IV. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH: SCOPE

Finally, the Office rejected claims 9(b), 13, 14 and 15 as having a scope broader than that which is enabled. The rejection was based on the contention that the specification does not reasonably enable the language "complete antitumor response." The Office's position is that one cannot extrapolate the teaching in the specification to the claims, because the degree of efficacy of a drug is not predictable, unless tested. Thus, although treatment of melanoma patients with small molecule inhibitors results in 86% patients having partial remission or less than partial remission, according to the Office, one cannot predict that treatment of melanoma patients with PD184352 would result in a "complete antitumor response" that is characterized by the "disappearance of all evidence of melanoma disease for at least one month."

These rejections are now moot based on the amendments to independent claim 9 and dependent claims 13-15. Amended claim 9 refers to an antitumor response with the same criteria, as set forth in original claim 9(a). Amended claim 10 adds an additional criterion ("disappearance of all evidence of melanoma disease for at least one month") that was initially included in 9b. Amended claim 10 is supported and enabled by the working examples in the specification where tumor remained in complete regression for **at least** 4 or 5 weeks (*e.g.*, paragraph bridging pages 8-9, describing Fig. 16B; see also page 53, lines 2-3). Fig. 18 shows that no tumors were detected starting from day 37 and for at least 71 days (*e.g.*, page 53, line 14). Fig. 20A shows that no tumors were detected starting from day 10 at least through day 36. Given the above, it is believed that the specification supports the scope of amended claim 10. Thus, this rejection is not applicable to amended claim 10, and may properly be withdrawn.

V. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are in condition for allowance, and respectfully requests early notice of such favorable action.

Examiner Davis is respectfully requested to contact the undersigned at (202) 344-8584 with any questions or comments if they will assist in the understanding this amendment and response.

If fees for the extra claims exceed the amount calculated herein, they may be charged to the **Deposit Account 22-0261**. Applicant has already paid the surcharge for multiple dependent claims. In the unlikely event that the Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to **Deposit Account 22-0261**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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